

(19) **FEDERAL REPUBLIC
OF GERMANY
(Unexamined)**

[Crest]

**GERMAN
PATENT AND
TRADEMARK OFFICE**

(12) **Patent Application**

(10) **DE 100 26 620 A1**

(21) **File No.:**

(22) **Filing date:**

(43) **Date laid open to the public:**

(51) **Int. Cl.:**

A 61 L 27/56

A 61 F 2/00

A 61 F 2/10

100 26 620.7

May 29, 2000

March 7, 2002

<p>(71) Applicant: Quelle, Gerhard, 69483 Wald-Michelbach, DE</p> <p>(61) Addition in: 101 26 246.9</p> <p>(72) Inventor: Request by one or more parties not to be named Quelle, Gerhard, 69483 Wald-Michelbach, DE</p>	<p>(56) Documents to be taken into consideration in evaluating patentability:</p> <p>DE197 01 912 C1 DE 39 41 023 C2 DE199 62 090 A1 DE 198 05 673 A1 DE 38 41 401 A1 DE 38 31 265 A1 DE 38 26 915 A1 DE 34 45 711 A1 US 5,571,182 A US 5,522,894 A US 5,492,697 A US 5,258,028 A EP 06 48 480 A2 EP 02 51 695 A2 WO 98 56 431 A1 WO 98 44 965 A1 WO 86 03 671 A1 WO 00 13 717 A1</p>
--	--

The following information has been taken from the documents submitted by the applicant.

(54) **Porous implants and particles**

(57) **The invention concerns porous particles and
microspheres and their use in technics and medicine.**

Description

[0001] Particles for technical applications or for use as medical implants have heretofore been primarily compact, irregularly shaped particles or round microspheres of only slight porosity, which nevertheless contain no inner cavity or recesses.

[0002] These compact particles or microspheres tend to sediment in low-viscosity solutions and even in high-viscosity solutions, either due to their lack of porosity or because no inner cavity is present or owing to a specific density of more than 1.0.

[0003] The product invention of particles or microspheres -- both terms will ordinarily be used in the same sense in the following description -- which are characterized by the porosity of the body or shell and/or at least one inner cavity, enables aqueous or nonaqueous solutions to be used as a depot or transport vehicle with or without significantly reduced concentrations of viscous components, such as polymeric polysaccharides or proteins, with very little or no sedimentation or migration.

[0004] The product invention, provided with functional chemical groups on the surface and the inner porous structure or on the inner cavity, allows special crosslinked and non-crosslinked, matrix-forming properties either in the depot fluid or transport fluid or at the site of administration.

[0005] Some examples of the advantages are improved formation of connective tissue, improved migration of connective-tissue cells into the implant, and improved survival rates of connective-tissue cells.

[0006] The pores and inner cavities of the particles and microspheres can be "loaded" with active compounds. This broadens the field of application from inactive to active implants. Such implants can contain more than one active ingredient with radioactive or nonradioactive properties. For example, the first active ingredient can be placed in the transport fluid, the second in the porous shell, and the third in one or more inner cavities.

[0007] A further example of the diverse applicability of the invention is to provide the surfaces of the particles with reactive sites that react particularly with, and bind specifically to, tumor cells and tumor tissues. After binding, the antitumor ingredient is released or the antitumor action initiated.

[0008] Examples of active or reactive material that can be loaded onto the exterior or the interior of the invented particles are: cells; stem cells; immunoreactive cells and components or epitopes; enzymes; proteins; peptides; viruses; viral components; microorganisms and components thereof; DNA; RNA; vectors; growth factors; growth inhibitors; antiviral, antimicrobial or radioactive components of alpha, beta or gamma radiation; sensitizers or reagents, triggered, released or activated by various types of external or internal means, such as chemical or biological reactions, physical pressure, sound, ultrasound, electromagnetic fields or ionizing radiation.

[0009] Such combinations yield, for example, improved medical, biochemical or analytical effects, or the immunologic reaction are [sic] directed more specifically, or tissue, organ or cellular immune tolerance is improved, as in the case of organ transplantation or degenerative autoimmune diseases.

[0010] Through the use of inner cavities, with or without recesses on the outer surface of the particles, or microspheres, with or without connecting channels through the nonporous or even porous shell, the product invention constitutes a suitable depot or transport medium and a protective vehicle for simple or complex implantable sensors and microsensors able to measure biochemical and other parameters, semiconductor devices, CPUs, bioreactor systems, micromachines, signal transmitters, signal receivers, energy-producing or energy-consuming devices, etc., for use in human, animal or plant organisms, microorganisms, extracellularly and intracellularly, e.g. mitochondria, nuclei, ribosomes, endoplasmic reticulum, for technical, medical, terrestrial, marine, atmospheric and space applications.

[0011] The particle invention can also be used as a two- or three-dimensional carrier and storer of non-holographic and holographic data, whether digitized or non-digitized. In combination with a suitable depot fluid or gel or matrix or an applied vacuum, the stability of the data can be controlled or improved.

[0012] The four size categories relative to the outer dimensions of the particles of this invention are as follows: (1) smaller than 0.1 micrometer; (2) 0.1-30 micrometers; (3) 30-1000 micrometers; (4) 1.0 mm to 100 mm.

[0013] The volume of the inner cavity of the particles can account for 0.001% to 99.9% of the overall volume of the particle or of the microspheres.

[0014] Typical but not exclusive examples of the type of material used for the invented particles are: organic or inorganic polymers or copolymers, organic or inorganic materials, metal, purified

cytoskeletons of single-celled algae and other organisms, materials whose density is 1.0 or less or greater than 1.0.

[0015] Depending on the size of the particles, the intended effects and the purposes of use, the different types of applications can, for example, range from injection, inhalation, spraying, swallowing, drinking, surgical or nonsurgical implantation or injection to being carried or worn on the outside of or near the body.

[0016] This invention also relates to biocompatible production compositions for (soft) tissue augmentation, for human or veterinary medical applications. A few examples of human and veterinary medical applications are: plastic/cosmetic and reconstructive surgery, (stress) incontinence, vesicourethral reflux, incontinence, gastroenterologic reflux diseases, vocal cord surgery and vocal chord paralysis, use of the product not, however, being limited to the above-cited examples. The product is delivered primarily by injection into the tissue in combination with a biocompatible transport fluid that has a positive effect on particle transport, delivery and deposition after delivery.

[0017] The site or place of deposition for the particles can be effected [syntax sic] intradermally, subdermally, subcutaneously, submucosally or intramuscularly, but is not limited to the above-cited tissues. The shape of the particles, regardless of surface structure, can be round, spherical or irregular; the particles contain a cavity and have a porous or nonporous shell. The particles as such can also have semipermeable and/or porous characteristics.

[0018] The product material can be comprised of natural or synthetic material if such a product comprises a cavity inside the regular or irregular shaped¹ particle shell.

[0019] For products with no cavity inside the particle, this patent is limited to particles comprising semipermeable and/or porous channels, if such particles are made of biocompatible materials such as organic synthetics, glass, metals, ceramic materials or natural constituents.

[0020] The particle size of the product depends on its surgical or nonsurgical use in human beings or animals, i.e., the sizes needed for plastic/cosmetic and reconstructive surgery are different from those needed for stress incontinence, gastroenterological reflux and other diseases. The size distribution is stated as "1 micrometer" or larger. The products can also be used nonsurgically, as in the case of wound or burn dressings.

¹TRANSLATOR'S NOTE: Sic, rather than "regularly or irregularly shaped."

[0021] The product composition with regard to the transport/delivery fluid depends on the specific body part in which the product is being implanted. Examples of transport fluids are water, aqueous buffer, collagen (from human beings or animals), biofermented human collagen, hyaluronic acid (from animals or plants or fermented), polysaccharides, or PVP or natural/synthetic oils, the aforesaid examples of transport fluids being non-limiting.

[0022] This patent also applies to the aforesaid particles comprising an empty inner cavity that can carry specifically developed (electronic) products. Such encapsulated (electronic/mechanical) products can be used to achieve specific local tissue characteristics of human beings or animals.

[0023] This patent also applies to the aforesaid particles comprising an inner cavity or particles that are porous/permeable, making it feasible for active or inactive components to be encased so that they can act therapeutically on certain tissues. Examples of such tissue interactions might be the treatment of localized tumors, vascular diseases and neurological disorders. Another example is use of the permeability/cavity of the product as the delivery system for certain active or inactive components that are encapsulated in the cavity and in the inner channels of the product, to enable the particles to act as (neuro)transmitter bridges in paralytic phenomena affecting specific nerve trunks or the spinal column.

[0024] The material of which the particles or microspheres are composed can possess special characteristics that cause it to react to or interact with sound; ultrasound; magnetic fields; electrical fields; microwaves; infrared, visible or UV light; or electromagnetic fields and radiation of even smaller wavelength.

[0025] The reactivity to such fields can be utilized in the form of frequency- or field-strength-dependent vibrations of the particles at the implant site to stimulate increased production of connective tissue, increased degeneration of fatty tissue, improvements or changes in the appearance of wrinkles and facial and body shapes, or the stimulation [syntax sic] or influencing of the functioning, activity or growth of nerve tissue. Or it can be utilized to trigger the release, excretion or reaction of loaded active or inactive components of the particles.

[0026] UK Patent Application No. 2,227,176 of Essek et al. relates to a microimplantation method for filling in sunken scars, asymmetrical "orbital floors" and superficial bone defects in reconstructive surgery, involving the use of microparticles about 20 to 3,000 microns in size that can be injected with a suitable physiological vehicle and a hypodermic needle and syringe into a predetermined location such as the base of a sunken scar, under the skin in depressed areas and

under the perichondrium or periosteum [sic] in the case of surface irregularities of bone and cartilage. Textured microparticles including silicon, polytetrafluoroethylenes, ceramic materials or other inert substances can be used. In cases where hard substances are necessary, biocompatible materials such as potassium salts, including hydroxyapatite or crystalline materials, biocompatible ceramic substances, biocompatible metals, such as stainless steel particles or glass, are used. Suitable physiological vehicles, including common salt, various kinds of starch, polysaccharides, and organic oils or fluids have been proposed.

[0027] US Patent No. 4,803,075 of Wallace et al. relates to an injectable implant composition for soft tissue augmentation, composed of an aqueous suspension of a special biocompatible, natural or synthetic polymer and a lubricant to improve the injectability of the biomaterial suspension.

[0028] US Patent No. 4,837,285 of Berg et al. relates to a collagen-based composition for soft-tissue expansion and repair in which the collagen is in the form of resorbable matrix beads with an average size of about 50 to 350 microns, with the collagen accounting for up to 10% of the volume of the beads.

[0029] US Patent No. 4,280,954 of Yannas et al. relates to a collagen-based composition for surgical applications that is formed by contacting collagen with a mucopolysaccharide under conditions in which they form a reaction product and then covalently crosslink² said reaction product.

[0030] US Patent No. 4,352,883 of Lim makes known a method for encapsulating a core material in the form of living tissue or individual cells by forming a capsule from polysaccharide glues that can be gelled to form a shape-retaining mass, it being exposed in the process to environmental changes, such as pH variation, or multivalent cations such as potassium.

[0031] Namiki, "Use of Teflon paste in urinary incontinence: a report on two cases," *Urol. Int.*, Vol. 39, pp. 280-282 (1984), discloses use of the injection of polytetrafluoroethylene paste into subdermal regions for the treatment of urinary incontinence.

[0032] Drobeck et al., "Histological observations of soft-tissue reactions to implanted multifaceted particles and disks of hydroxyapatite," *Journal of Oral Maxillofacial Surgery*, Vol. 42, pp. 143-149 (1984), describes the effect on soft tissues of short-term and long-term hydroxyapatite ceramic implants implanted subcutaneously in rats and subperiostally in dogs. The inventions

²TRANSLATOR'S NOTE: Sic, rather than "crosslinking."

consisted of implanted hydroxyapatite in different sizes and shapes for a period of seven days to six years [syntax sic] to determine whether migration and/or inflammation occurred.

[0033] Misiek et al. discloses [sic] in "Soft-tissue reaction to differently shaped hydroxyapatite particles," *Journal of Oral [and] Maxillofacial Surgery*, Vol. 42, pp. 150-160 (1984), that implanting hydroxyapatite in the form of sharp-edged or round particles in soft tissues in the pockets of the oral cavity can result in inflammatory reactions at the implant site with both particle shapes. The particles weighed 0.5 g in each case. However, inflammation developed more rapidly at the site where the round hydroxyapatite particles were implanted.

[0034] Shimizu, in "Subcutaneous tissue responses in the rat to the injection of fine particles of synthetic hydroxyapatite ceramic," *Biomedical Research*, Vol. 9, No. 2, pp. 95-111 (1989), reports that subcutaneous injections and tissue distribution of fine hydroxyapatite particles about 0.65 to a few microns in diameter were phagocytosed in extremely early stages [sentence sic]. Larger particles several microns in diameter were not phagocytosed, but they were surrounded by numerous macrophages and multinucleated giant cells. It was also observed that the minor tissue reactions to hydroxyapatite particles were essentially a nonspecific foreign-body reaction with no cell or tissue damage.

[0035] R.A. Appel, "The artificial urinary sphincter and periurethral injections," *Obstetrics and Gynecology Report*, Vol. 2, No. 3, pp. 334-342 (1990), is a survey article that describes the various treatment modalities for weakness of the urinary sphincter, including the use of injectable material such as polytetrafluoroethylene micropolymer particles about 4 to 100 microns in size and irregular in shape, with glycerin and polysorbate.

[0036] Another periurethrally injectable agent is high-purity collagen from cattle hide, crosslinked with glutaraldehyde and distributed in phosphate-buffered salt solution.

[0037] Politano et al., "Periurethral Teflon injection in urinary incontinence," *The Journal of Urology*, Vol. 111, pp. 180-183 (1974), describes the use of a polytetrahydrofluoroethylene paste that is injected into the urethra and the periurethral tissue to impart volume to this tissue in order to restore urinary control in female and male patients suffering from urinary incontinence.

[0038] Malizia et al., "Migration and granulomatous reaction after periurethral injection of Polytef (Teflon)," *Journal of the American Medical Association*, Vol. 251, No. 24, pp. 3277-3281, June 22-29 (1984), reports that although patients with urinary incontinence were treated successfully

by periurethral injection of polytetrafluoroethylene paste, a study performed in continent animals demonstrated that polytetrafluoroethylene particles migrated away from the test site.

[0039] Claes et al., "Pulmonary migration following periurethral polytetrafluoroethylene injection for urinary incontinence," *The Journal of Urology*, Vol. 142, pp. 821-2 (September 1989), confirms Malizia's investigation by reporting a case of clinically significant migration after periurethral injection of polytetrafluoroethylene paste particles into the lungs.

[0040] Ersek et al., "Bioplastic: a newly created copolymer microparticle promises durability for soft-tissue expansion," *Plastic and Reconstructive Surgery*, Vol. 87, No. 4, pp. 693-702 (April 1991), describes the use of a two-phase copolymer made of fully polymerized and vulcanized methyl methylpolysiloxane mixed with a "plasdone" hydrogel and used to treat cleft lip, sunken scars due to chicken pox and depressed areas due to liposuction, and forehead wrinkles, and for soft-tissue filling for thin lips. It was found that the two-phase copolymer particles had neither migrated nor been resorbed by the body, were structured, and had particle sizes of 100-600 microns.

[0041] Lemperle et al., "PMMA microspheres for intradermal implantation: Part I. Animal studies," *Annals of Plastic Surgery*, Vol. 26, No. 1, pp. 57-63 (1991), describes the use of polymethylacrylate microspheres with a particle size of 10 to 63 microns in diameter to amend small flaws in the dermis in order to treat wrinkles and acne scars.

[0042] Kresa et al., "Hydron gel implants in vocal cords," *Otolaryngology Head and Neck Surgery*, Vol. 98, No. 3, pp. 242-245 (March 1988), describes a method for treating vocal cord correction in cases of inadequate glottal closure by inserting into the vocal cords a shaped hydrophilic gel implant that has first been dried to a glassy, hard consistency.

[0043] Hirano et al., "Transcutaneous intrafold injection for unilateral vocal cord paralysis: functional results," *Ann. Otol. Rhinol. Laryngol.*, Vol. 99, pp. 598-604 (1990), describes the technique of transcutaneous "intracord" silicon injection to treat glottal incompetence due to unilateral vocal cord paralysis. The silicon injection is administered to the patient in a supine position under local anesthesia, the needle being inserted through the cricothyroid region.

[0044] Hill et al., "Autologous fat injection for vocal cord medialization in the canine larynx," *Laryngoscope*, Vol. 101, pp. 344-348 (April 1991), describes the use of autologous fat as an alternative to Teflon collagen as an implant material for vocal cord medialization, with a view toward its use as an alternative to non-autologous injectable material to fill out vocal cords.

[0045] Mikaelian et al., "Lipoinjection for unilateral vocal cord paralysis," *Laryngoscope*, Vol. 101, pp. 4654-68 (May 1991) reports that in the customary procedure of injecting Teflon paste to improve vocal strength in unilateral vocal cord paralysis, has [sic] a number of disadvantages, including respiratory impairment due to excessive Teflon injection and unsatisfactory speech quality. This method of fat injection, in which fat is usually taken from the abdominal wall, seems to give the treated cord a soft consistency while still allowing it to retain its vibratory properties. The injected fat is an autologous material that can be re-extracted if too much is injected.

[0046] Strasnick et al., "Transcutaneous Teflon® injection for unilateral vocal cord paralysis. An update," *Laryngoscope*, Vol. 101, pp. 785-787 (July 1991), describes Teflon injection to restore vocal cord competence in cases of paralytic paraphonia.

[0047] The biocompatible material contains a matrix of soft, round, spherical (insofar as possible), finely separated particles of biocompatible ceramic material, disposed close together or in mutual contact, which serves as a framework or grid for autogenous, three-dimensional, randomly arranged, non-scarring soft-tissue growth at the augmentation site. The augmenting material can be distributed homogeneously, e.g. in a biocompatible, resorbable, glidable gel carrier encasing a polysaccharide, for example. This makes for better transport of the augmenting material on injection into the tissue site where augmentation is desired. The augmenting material is particularly well suited for urethral sphincter augmentation, for the treatment of incontinence, for filling in depressed areas in soft tissue, for generating soft-tissue bubbles, for the treatment of unilateral vocal cord paralysis, and for breast implants. It can be injected or implanted in or beneath the skin.

Claims

1. A biocompatible material for cell and tissue implantation, **characterized in that** the material is composed of irregular or round, spherical particles or microspheres, substantially nonresorbable, with a semitransparent, transparent or porous outer shell and one or more inner cavities.
2. The material as recited in claim 1, characterized in that its composition can be comprised of natural, metallic or synthetic material or of biological origin [syntax sic], particularly the purified cytoskeletons of single-celled algae or organisms.
3. The material as recited in claims 1 and 2, characterized in that its outer shell is compact, nonporous and impermeable.
4. The material as recited in one of claims 1, 2 and 3, characterized in that said particles or microspheres are porous but contain no cavities.
5. The material as recited in one of claims 1, 2, 3 and 4, characterized in that said inner cavity and/or the porous portions account for a volume of at least 0.001% to 99.9% of the overall volume.
6. The material as recited in one of claims 1, 2, 3, 4 and 5, characterized in that the size of the particles and microspheres is 0.01 micrometer to 100 mm.
7. The material as recited in one of claims 1, 2, 3, 4, 5 and 6, characterized in that said material is resorbable.
8. The material as recited in one of claims 1, 2, 3, 4, 5, 6 and 7, characterized in that the density of said material is between 0.2 and 8.0.
9. The material as recited in one of claims 1, 2, 3, 4, 5, 7 and 8, characterized in that said material is used as tissue-augmenting material in sizes of more than 20 micrometers to 10 mm.
10. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8 and 9, characterized in that the outer surface of said material or the porous material or the inner surface of the shell is modified by means of covalent or non-covalent bonds, with one or more types of molecular side chains that are capable of forming bonds with specific tissue or cell regions or with subcellular regions or with positive and/or negative, polar or nonpolar groups of specific organic or inorganic substances.

11. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, characterized in that the outer surface of said material or the porous material or the inner surface of the shell is modified by means of covalent or non-covalent bonds with crosslinking agents, with the ability to crosslink either in the depot fluid, in the transport fluid or at the administration site.
12. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11, characterized in that said material is used in combination with a depot, transport or administering fluid.
13. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12, characterized in that said fluid is composed of water, aqueous buffer of synthetic or natural polymers in aqueous solution, or of nonaqueous fluids, collagen (or human or animal origin), biofermented human or animal collagen, hyaluronic acid (of animal, fermented or plant origin), polysaccharides, PVP or natural/synthetic oils.
14. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13, characterized in that the percentage volume of said particles in the transport/administering fluid ranges from more than 0.0% to 100%, no transport fluid being present when the final product is 100% particles.
15. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that either the transport fluid, the outside of the particles and microspheres or the inner pores and the cavity are loaded with one or more active or inactive components, particularly with cells, cell components, stem cells, immunoreactive cells and components, epitopes, enzymes, proteins, peptides, viruses, viral pieces, microorganisms and pieces thereof, DNA, RNA, vectors, growth factors, growth inhibitors, antiviral, antimicrobial radioactive components for alpha, beta or gamma radiation, sensitizers.
16. The material as recited in claim 15, characterized in that the release or activation of the reactive components is triggered by physical forces, biochemical reactions and electromagnetic fields or radiation.
17. The material as recited in claim 16, characterized in that depending on the administration site, said material interacts with externally applied forces and is placed in vibration, as by sound, ultrasound, magnetic fields, electrical fields, microwaves, infrared or other electromagnetic waves, in order to increase the production of connective tissue or the degradation of fatty tissue or to influence the functioning of nerve tissues, including that of acupuncture sites.

18. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that the inner space is used to encapsulate or house simple or complex devices, particularly sensors, microsensors in order to measure biochemical or other parameters, microsurgical instruments, semiconductor devices, CPUs, bioreactor systems, micromachines, signal transmitters, signal receivers, energy-producing and -consuming systems, or a combination thereof.
19. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used as a two- or three-dimensional carrier and storage system for implanted memory chips, non-holographic and holographic data, digitized or non-digitized. The additional use of radical traps in a fluid, gel or matrix or under vacuum extends the stability of the stored data. [Two-sentence claim sic.]
20. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is provided with reactive sites that contact tumor cells and tumor tissues in order to localize them and are loaded with antitumor substances for tumor and cancer therapy.
21. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it can be introduced by various methods of administration, either with or without transport fluid, particularly by injection, by surgical or nonsurgical implantation or through natural body orifices, by spraying, inhalation, swallowing, drinking.
22. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used, together with natural or synthetic components for external use, as a cosmetic product or as an ingredient in cosmetic products.
23. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used, not for medical products, but for cosmetic tissue augmentation.
24. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used for diagnostic purposes.
25. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used for human and veterinary medical indications.
26. The material as recited in one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14, characterized in that it is used as an implant for intradermal, subdermal, mucosal, subcutaneous or muscular disorders.